Pilot single-arm clinical trial to evaluate the efficacy, PK interactions and safety of dolutegravir plus 2 NRTIs in HIV-1-infected solid organ transplant patients

Code: DTG-SOT

Version 1.0, 8th May 2017

EudraCT: 2017-000469-62

Sponsor: **Fundació Clínic per a la Recerca Biomèdica**
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SIGNATURES

The coordinating investigator and the sponsor of the study:

Pilot single-arm clinical trial to evaluate the efficacy, PK interactions and safety of dolutegravir plus 2 NRTIs in HIV-1-infected solid organ transplant patients

Declare that this study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) and the applicable regulatory requirements.

Modifications to this protocol must be submitted prior agreement of the coordinator investigator and sponsor.

Coordinating Investigators:

Jose M. Miro Meda (PI), MD, PhD
Christian Manzardo (Co-PI), MD, PhD

Signatures and Date:

Sponsor: Fundació Clínic per a la Recerca Biomèdica
C/ Rosselló, 149-153 08036 Barcelona, Spain

Signature and Date:

1 GENERAL INFORMATION

1.1 TITLE

Pilot single-arm clinical trial to evaluate the efficacy, PK interactions and safety of dolutegravir plus 2 NRTIs in HIV-1-infected solid organ transplant patients.

1.2 CODE

EudraCT number: 2017-000469-62
Study Code: DTG-SOT

1.3 PROTOCOL VERSION AND DATE

Version 1.0, May 8, 2017
Any modification of the protocol must also bear the amendment number and date.

1.4 SPONSOR

Fundació Clínic per a la Recerca Biomèdica
C/ Rosselló, 149-153 08036 Barcelona
Tel.: (93) 227 57 07
e-mail: fclinic@clinic.ub.es.

Person authorized by the sponsor to sign the protocol and amendments:
Jose M. Miro Meda, MD, PhD

1.5 MONITOR

CTU-CLINIC-Clinical Trial Unit
C/ Rosselló, 138, bajos y
C/Mallorca 183.
Fax: 93 227 9877
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1.6 COORDINATING INVESTIGATOR

Jose M. Miro Meda, MD, PhD

1.7 SITES AND INVESTIGATORS

This unicentric study will be performed in:

- Hospital Clínic de Barcelona

1.8 TECHNICAL SERVICES INVOLVED

Biochemistry; Hematology, quantitative HIV-1 RNA levels and CD4 counts will be performed in the Central laboratory of Hospital Clinic (T +34 2275400 Ext 3328).

Dolutegravir, Raltegravir and immunosuppressants plasma levels will be performed at CDB (Centre de Diagnòstic Biomèdic) Bioquímic and Molecular Genétic Unit, Hospital Clínic, Barcelona, Spain (T. +34 2275400 Ext 3328, email: mbrunet@clinic.ub.es)

CONTENTS

2 ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AR	Adverse reaction
BP	blood pressure
cART	Combination Antiretroviral Therapy
CTA	Clinical Trial Agreement
DSMB	Data Safety Monitoring Board
DTG	Dolutegravir
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drugs Administration
GCP	Good Clinical Practice
GP	General Practitioner
HAART	Highly active antiretroviral therapy
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HC	Clínic Hospital
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference of Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethic Comitte
iv	Intravenous
MS	Mass spectrometry
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PBMCs	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PK	Pharmacokinetics
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
pVL	Plasma viral load
QD	Once-a-day
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOT	Solid Organ Transplant
SUSAR	Suspected Unexpected Serious Adverse Reaction
RAL	Raltegravir
TDF	Tenofovir Fumarate
TMF	Trial Master File

3 SUMMARY

Objectives:

The aims of this study are to obtain pharmacokinetic data on interactions between DTG and immunosuppressant drugs (Cyclosporine A, Tacrolimus, Syrolimus and Mycophenolic acid) in SOT recipients To provide proof of principle data that DTG plus 2 NUCs is safe and effective in HIV-infected SOT recipients.

Methods:

Study Design: Single-arm clinical trial. Twenty HIV-infected SOT recipients (10 liver transplant recipients, 8 renal transplant recipients and 2 heart transplant recipients) receiving TDF/FTC or ABC/3TC plus raltegravir will be switched to DTG plus the same 2 NUCs. Depending on the results of the proviral genotyping, patients receiving a third drug (e.g. rilpivirine) other than raltegravir can be also be considered for switching to DTG plus 2 NUCs. Whenever possible, the ABC+3TC combination will be the preferred NUCs. All patients will be followed over 48 weeks. All SOT recipients will be proposed to perform RAL (or other antiretroviral drug) and immunosuppressor drugs 24-hour pharmacokinetic profiles before the switch, and DTG and immunosuppressor drugs 24-hour pharmacokinetic profiles 12 weeks after switching. The aim is to detect any possible drug-drug interactions between DTG and widely used immunosuppressant drugs (Cyclosporine A, Tacrolimus, Syrolimus and Mycophenolic acid).

Inclusion/Exclusion criteria:

Inclusion criteria:

1. HIV patients >18 years old who provide signed and dated informed consent;
2. Males and females;
3. SOT recipients (heart, liver or kidney);
4. On stable ART for ≥6 months preceding the screening visit;

5. Plasma HIV RNA <50 cop/ml for 12 months (2 tests separated by at least 12 months with no viral load >50 between determinations);
6. Absence of major reverse transcriptase or integrase gene mutations affecting study drug efficacy by proviral DNA sequencing.

Exclusion criteria:

1. HIV patients who have stopped ART due to virological failure;
2. HIV patients who require treatment with DTG contraindicated medications;
3. History or presence of an allergy or intolerance to the study drug;
4. Active opportunistic infection;
5. Neoplasms requiring chemotherapy.
6. Pregnancy or breast feeding or planned pregnancy during the study period
7. Any other contraindication to study drugs.

Number of Patients

Twenty (10 liver transplant recipients, 8 renal transplant recipients and 2 heart transplant recipients)

4 BACKGROUND INFORMATION

With the advent of combined antiretroviral therapy (cART), patients infected with the type 1 human immunodeficiency virus (HIV) are now living longer and dying of illnesses other than acquired immunodeficiency syndrome. Although the outcome of solid organ transplantation (SOT) in HIV-infected recipients was poorer than in HIV-negative recipients in the pre-HAART era, more recent evidence has demonstrated comparable results in both populations [1-3]. Currently, SOT can be performed safely in selected HIV-1-infected patients [4-6]. However, a number of issues persist regarding patient selection, postoperative management, and pharmacokinetic and pharmacodynamic interactions between antiretroviral and immunosuppressive agents. A key challenge in the post-transplant period is the management of pharmacokinetic interactions between immunosuppressive and

antiretroviral drugs, particularly HIV protease inhibitors (PIs), which involve a higher risk of allograft rejection and drug toxicity [7]. Frequent monitoring of the levels of calcineurin inhibitors (e.g., tacrolimus or cyclosporine A) is necessary when PIs are introduced or withdrawn in HIV-infected SOT recipients, because they are potent CYP450 inhibitors. Furthermore, the pharmacokinetics of corticosteroids and mTOR inhibitors can be affected by PIs. In contrast, non-nucleoside reverse transcriptase inhibitors (NNRTI), such as efavirenz and nevirapine, which are commonly used in HAART regimens, are strong CYP450 inducers and decrease serum levels of calcineurin inhibitors, resulting in the need to increase their dose to prevent allograft rejection. Raltegravir (RAL) was the first HIV-1 integrase inhibitor to be approved for clinical practice [8]. A favorable pharmacokinetic profile has been demonstrated in HIV-infected SOT recipients co-treated with RAL and calcineurin inhibitors (cyclosporine, tacrolimus), mTOR inhibitors, and corticosteroids [7,9], indicating that RAL is probably safe and efficacious in HIV-infected SOT recipients [9]. However, because of its low genetic barrier, RAL should be administered in general terms with two nucleot(s)ide analogs such as TDF/FTC or 3TC/ABC. Tenofovir is an acyclic nucleotide analog reverse-transcriptase inhibitor structurally similar to the nephrotoxic drugs adefovir and cidofovir. Tenofovir is widely used to treat HIV infection and approved for the treatment of the hepatitis B virus. Despite initial cell culture and clinical trial results supporting the renal safety of tenofovir, its clinical use is associated with a low, albeit significant, risk of kidney injury [10,11]. The proximal tubular cell secretion of tenofovir explains the accumulation of the drug in these mitochondria-rich cells. Tenofovir nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease. Withdrawal of the drug leads to an improvement of analytical parameters that may only be partial. Newer, structurally-similar molecular derivatives that do not accumulate in proximal tubules are under study, but are not yet commercially available. SOT recipients are prone to renal dysfunction because of pre-existing conditions such as diabetes, hypertension or cirrhosis and because of the

nephrotoxicity of immunosuppressive drugs, especially calcineurin inhibitors. In this sense, a TDF-free cART regimen would be desirable in the post-transplant period. Spanish guidelines consider ABC/3TC plus an integrase inhibitor to be a preferable combination for kidney transplant recipients because it does not affect renal function [12].

However, there are no published clinical data supporting this suggestion. Dolutegravir (DTG) is a novel QD integrase inhibitor approved by FDA and EMA both for antiretroviral-naïve and treatment-experienced patients. It is metabolized mainly by the UGTA1 liver enzyme and, only in a small percentage (less than 10%), by CYP3A4. For these reasons, it is expected to have a favorable drug-drug interaction profile, at least comparable to RAL. DTG+3TC+TDF/ABC may become the standard of care for HIV-infected SOT recipients because of its low drug-drug interaction potential, its high barrier to resistance (higher than RAL) and its convenience (QD vs. BID for RAL).

4.1 HYPOTHESIS

1. DTG is safe and effective in HIV- infected SOT treatment.

2. DTG has few PK interactions with commonly used immunosuppressant drugs.

3. ABC/3TC NRTI backbone leads to a better safety profile, especially in terms renal safety, compared with TDF/FTC in HIV-infected SOT recipients.

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5 TRIAL OBJECTIVE AND PURPOSE

5.1 PRIMARY OBJECTIVES

1. To obtain pharmacokinetic data on interactions between DTG and immunosuppressant drugs (Cyclosporine A, Tacrolimus, Syrolimus and Mycophenolic acid) in SOT recipients;

2. To provide proof of principle data that DTG plus 2 NRTIs is safe and effective in HIV-infected SOT recipients.

5.2 SECONDARY OBJECTIVES

1. To assess the development of viral resistance in subjects experiencing virological failure;

2. To assess the changes in CD4+ cell count in peripheral blood;

3. To assess the changes in lipid profile (triglycerides, total, LDL- and HDL-cholesterol);

4. To assess renal function in HIV SOT patients.

6 TRIAL DESIGN

6.1 TYPE OF TRIAL

Phase IV, single-center, open-label, single arm clinical trial.

6.2 DESCRIPTION OF THE DESIGN

Type of Study: Single-arm clinical trial.

Twenty HIV-infected SOT recipients (10 liver transplant recipients, 8 renal transplant recipients and 2 heart transplant recipients) receiving TDF/FTC or ABC/3TC plus raltegravir (or other third drug) will be switched to DTG plus the same 2 NRTIs. Patients who switched to 2 NRTIs plus DTG in the last 48 weeks will be also eligible

for the study. Whenever possible, the ABC+3TC combination will be the preferred NRTIs. All patients will be followed over 48 weeks from switching.

To accomplish with the Primary Objectives:

1. **Pharmacokinetic (PK) studies:** All SOT recipients will be proposed to perform RAL (or other antiretrovirals) and immunosuppressor drugs 24-hour pharmacokinetic profiles before the switch, and DTG and immunosuppressor drugs 24-hour pharmacokinetic profiles 2 weeks after switching. Patients already receiving 2NRTIs plus DTG will be proposed to perform only DTG and IS PK study. The aim is to detect any possible drug-drug interactions between DTG and widely-used immunosuppressant drugs (IS) (Cyclosporine A , Tacrolimus, Syrolimus and Mycophenolic acid).

Procedures:

Patients will be electively admitted to the Hospital (Infectious Disease Service) during 24 hours approximately.

1. A 24- hour PK will be performed.
2. A peripheral venous line will be positioned by a trained nurse.
3. RAL (or other ARV) or DTG as long as IS plasma concentrations before and at 0.5, 1, 2, 4, 8, 10, 12 and 24 hours after the ARV and IS administration will be determined.
   Three 10 mL EDTA tubes will be extracted at each timepoint.

Safety and effectiveness of DTG in SOT setting and Secondary Endpoints (see Section 8 for details) :

- At w0, w12, w24, w36 and w48 physical examination, including blood pressure and wheight will be performed.
- At same timepoints the following parameters will be measured**:**

  - CD4+/CD8 T cell count
  - Plasma HIV-1 levels.

- Blood chemistry (including triglycerides, total, HDL- and LDL-cholesterol and CK)
- Hematology
- Creatinine, eGFR (CKD-EPI)
- Basic urine profile, including glycosuria, proteinuria and creatinine/protein.

In case of viral rebound (confirmed detectable viral RNA in 2 susequent determinations > 50 cp/mL) a genotypic test and viral tropism will be performed.

6.3 MEASURES TO AVOID BIAS

6.3.1 Randomization

Not applicable, since it is a single arm clinical trial.

6.3.2 Stratification

Not applicable, since it is a single arm clinical trial.

6.3.3 Blinding

Not applicable since it is an open clinical trial.

6.4 FORESEEN CALENDAR

- First patient first visit: August 2017
- Inclusion period: 12 months
- Follow-up period: At last 48 weeks (12 months)
- Last patient last visit: August 2019 (End of study)
- Final report submission: November, 2019

6.5 END OF TRIAL

Stopping rules will be based on the observation of an unexpected high proportion of individuals experiencing SAE or any grade ≥3 local or systemic events judged definitely or probably related to any of the study drugs administration.

If two or more study participants develop a clinically similar SAE or grade 3 local or systemic event, judged definitely, or probably related to the investigational medicinal products (IMP)s, a review by the Scientific Committee will be requested. The study will be suspended pending review of all safety data. Following this review, the Scientific Committee will make a recommendation to the Principal Investigator and Sponsor regarding continuation of the study.
In addition, if more than 50% of participants withdraw from the Scientific Committee will discuss a premature stop of the trial.

The date of the end of the trial will be to the last visit of the last patient.

6.5.1 Early study suspension

If the study must be interrupted prematurely, all non-used materials should be returned to the sponsor. The principal investigator will keep the investigator file and the completed CRF.

In case there were no patients included in the study, the sponsor will take care of all materials.

6.6 SOURCE DATA

Source documents are the patient's medical records including routine laboratory results obtained from blood tests. A scanned copy of all source documents will be included in the patient's medical chart, when possible; in all cases, these source documents will be included in the investigator site file.

Study data will be collected through the HIV database of the AIDS functional Unit.

All investigational results from analysis performed from stored samples (virological, immunological results as well as PK determinations) will be recorded in electronic databases. Once the trial is finished, all databases will be unified.

Information regarding safety and tolerability will be reported by the physician in the patient's electronic medical history, which will be reviewed by the attending physician for grading and assessment of causality/imputability.

7 TRIAL INVESTIGATIONAL PRODUCT(S)

7.1 TREATMENTS: SUPPLY, PACKAGING, LABELING AND STORAGE

7.1.1 All investigational products will be stored at the Pharmacy Service of Hospital Clinic of Barcelona.

7.2 DOSE, INTERVAL, ROUTE AND METHOD OF ADMINISTRATION

The drugs under study will be administered orally. The daily doses will be:

- Lamivudine 300 mg + Abacavir 600 mg + dolutegravir 50 mg / 24h (Triumeq®), 1 tablet once daily; -

-Emtricitabine 200 mg/Tenofovir 245mg (Truvada®, 1 tablet once daily)
- Dolutegravir 50 mg (Tivicay®, 1 tablet once daily)

7.3 DRUG ACCOUNTABILITY

During the study, an accountability log, dispensing log and log of used boxes will be kept for all IMPs. These logs will be monitored according to Good Clinical Practice (GPC) guidelines.

Labeling of investigational medicinal drug will be done in according to applicable regulations (Directive 2003/94/CE, annex 13 GMP).

Sample of the label:

Código Protocolo: DGT-SOT
Nº EudraCT: 2017-000469-62
Promotor: Fundació Clinic per a la Recerca Biomèdica
Investigador principar: JM Miró
Contiene: príncipio activo / (dosificación) mg
Nombre comercial/ vía oral / comprimidoss
Código paciente:_____
Lote nº Y fecha de caducidad (consultar en la caja)
Conservar a temperatura ambiente y fuera del alcance de los niños
Solo uso en ensayo clínico

7.4 CONCOMITANT TREATMENTS

7.4.1 Other treatments

All participants will be discouraged to initiate any concomitant treatment without the knowledge and permission of the investigator. Patients will be discouraged of taking strong CYP3A4 inhibitors (ritonavir, cobicistat, atazanavir, ketoconazole, itraconazole, voriconazole, clarithromycin, telithromycin) or CYP3A4 inducers (nevirapie, efavirenz, etravirine, rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbitalk, St. John's Worth).

7.5 COMPLIANCE

Antiretroviral treatment adherence will be self-reported. No pill count will be performed to assess compliance.

8 SELECTION AND WITHDRAWAL OF SUBJECTS (INCLUSION/EXCLUSION CRITERIA)

8.1 INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

1. HIV patients >18 years old who provide signed and dated informed consent;
2. Males and females;
3. SOT recipients (heart, liver or kidney);
4. On stable ART for ≥6 months preceding the screening visit;
5. Plasma HIV RNA <50 cop/ml for 12 months (2 tests separated by at least 12 months with no viral load >50 between determinations);
6. Negative HLA B5701 in recipient (and donor, if available);
7. Absence of major reverse transcriptase or integrase gene mutations affecting study drug efficacy by proviral DNA sequencing.

Exclusion criteria:

1. HIV patients who have stopped ART due to virological failure;
2. HIV patients who require treatment with DTG contraindicated medications (i.e., current treatment with rifampin, phenytoin, phenobarbital, carbamazepine, oxcarbazepine);
3. History or presence of an allergy or intolerance to the study drug;
4. Active opportunistic infection;
5. Neoplasms requiring chemotherapy;
6. Pregnancy or breast feeding or planned pregnancy during the study period
7. Any other contraindication to study drugs.

* Female subjects of childbearing potential must not be pregnant, not be planning a pregnancy or breast-feeding. Sexually active women must be willing to use two approved methods of contraception (including condoms, diaphragm, spermicides, hormonal methods and/or intrauterine devices) from screening until 28 days after last immunization. Sexually active men in heterosexual relationships must be willing

to use two approved method of contraception with their partners from screening until 28 days after last immunization.

8.2 SUBJECT WITHDRAWAL CRITERIA

8.2.1 Related to Dolutegravir-containing regimens

Any individual for who is being considered for discontinuation or postponement of vaccinations will be discussed with the trial team.

- Ineligibility (either arising during the study or retrospective having been overlooked at screening).

- A disease, condition or an adverse event (including clinically significant abnormal laboratory values; see below) that develops, regardless of relationship to the study products, if, in the opinion of the principal investigator or designee, further vaccinations would jeopardize the safety of the patient.

- Hematology

    - Hemoglobin < 8.0 g/dl
    - Absolute Neutrophil Count (ANC) ≤ 1000 /mm^3 (≤ 1 x 10^9 /l)
    - Absolute Lymphocyte Count (ALC) ≤ 500 /mm^3 (≤ 1 x 10^9 /l)
    - Platelets ≤ 50.000 /mm^3, ≥ 550,000 /mm^3 (≤ 50 /L, ≥ 550 /l)

- Biochemistry

    - Creatinine > 1.5 x ULN
    - AST > 5 x ULN
    - ALT > 5x ULN

- Pregnancy.

- Significant non-compliance with cART regimen or study requirements.

- A serious adverse event judged to be possibly, probably or definitely related to vaccination.

- An adverse event which requires discontinuation of the study product or results in inability to continue to comply with study procedures.

- Loss to follow up.
- The safety of the volunteer would be jeopardized in the opinion of the investigator or sponsor.
- Investigator discretion.
- Significant protocol deviation.
- Disease progression, including virological failure (defined as a rebound in at least two consecutive determinations of pVL > 2,000 copies/ml after suppression), which requires discontinuation or modification of the study medication or results in inability to continue to comply with study procedures.
- Consent withdrawn.

8.2.2 Early subject withdrawal

The patients will complete the clinical study before the stipulated time in the following circumstances:

- Concurrent process or illness which in the opinion of the investigator requires the withdrawal of the patient.
- Protocol deviation which in the opinion of the sponsor requires the withdrawal of the patient.
- The patient does not wish to continue in the study.
- Other

8.2.3 Medical approach to withdrawal

In all cases, 'end of study form' is to be filled. Detailed information will be given about the date and reasons of the discontinuation to the sponsor. The investigator will facilitate the necessary medical support to the patient.

8.2.4 Follow-up after early withdrawal

That is, as a general rule, all patients who discontinue treatment prematurely will undergo a clinical examination and all tests specified in the visit.

In case early withdrawal happens while patient is receiving IMP, a follow-up of 28 days after the last IMP dose will be performed for AEs collection.

9 TRIAL CONDUCTION AND RESPONSE EVALUATION

Clinical Procedures: Physical examination, assessment of adverse events, and adherence to treatment at each study visit.

Laboratory Tests:

- Proviral HIV DNA sequencing before switching therapy: **w0**
- Plasma HIV RNA: **w0, w4, w12, w24, and w48.** HIV RNA will be monitored in a central laboratory
- Resistance testing: Any patient with a viral load above 50 copies/mL will have an attempted phenotype/genotype testing on day 1 (first day with a viral load >50 copies/mL) and at the time of confirmed failure samples (including those with <400 c/mL)

- CD4+ cell count at **w0**, **w12, w24, w36** and **w48**
- Blood chemistry (including triglycerides, total, HDL- and LDL-cholesterol)
- Hematology
- Creatinine, eGFR (CKD-EPI)
- Basic urine profile, including glycosuria, proteinuria and creatinine/protein.
- RAL and immunosuppressant 24-hour PK profile before the switch, and DTG and immunosuppressant 24-hour pharmacokinetic profile 2 weeks after switching in SOT recipients.

9.1 LONG-TERM FOLLOW-UP

After end-of-study, participants will continue with cART and return to standard clinical care in consultation with their doctor, in HIV units from HGTIP and HC. All participants will be followed-up annually for 5 years in regards to:

- Safety
- HIV related information

9.2 PROCEDURES FOR EVALUATION OF RESPONSE

9.2.1 Clinical record and physical exam

Demographic and HIV infection-related data will be collected in order to characterize the study population (sex, age, time since HIV transmission to treatment initiation, Fiebig stage at HIV diagnosis, risk factor and history of opportunistic infections or tumors).

Appearance of clinical adverse events will be recorded all over the study. A complete physical examination will be performed at the baseline visit, including weight and height. In the follow-up visits, a physical exam will be performed following schedule described in attachment J (Schedule of procedures).

9.2.2 Laboratory tests

Patients will fast for at least 8 hours prior to assessment, in the points specified in the schedule of procedures of the study (attachment J), except for RMD_1 assessment that will be performed in the evening previous RMD_1 administration. The following parameters will be quantified, as needed:

- **Hematology:**
  - Hematocrit
  - Red blood cell count
  - Hemoglobin
  - Leucocytes
  - Lymphocyte
  - Platelet count

- **Blood biochemistry:**
  - Glucose
  - Urea
  - Creatinine
  - Ionogramme: sodium, potassium
  - Total Bilirubin
  - Total protein

Albumin
Liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-GT, alkaline phosphatase
Estimated glomerular filtration rate (CKD-EPI)
Creatinin Kinase (CK)

Lipid profile: Triglycerides, Cholesterol (HDL, LDL and total)

Extra ions: Magnesium, phosphate and calcium

- **Pregnancy test in women (test strip)**

- **Immunology:**
  CD4 lymphocytes count
  CD4 lymphocytes percentage
  CD8 lymphocytes count
  CD8 lymphocytes percentage.

Virology.: Viral Load (HIV-RNA)

Note: Before the beginning of the study, all labs will facilitate to the sponsor and to the investigator a list of the reference normal values of the parameters assessed.

- **Specific Lab Procedures**

Laboratory techniques used for PK:

CsA and MPA levels will be determined by immunoassay (EMIT200, Siemens).
TAC and sirolimus (or everolimus) whole blood concentrations FK levels will be determined using a validated ultra-High performance liquid chromatography–tandem mass spectrometry analytical method
chemiluminescent microparticle immunoassay (ARCHITECT i 2000 SR, Abbott).

RAL plasma levels will quantified by a validated method of liquid chromatography coupled with fluorescence detection after liquid-liquid extraction.and

DTG Plasma concentrations will be analyzed by liquid chromatography coupled with Triple quadrupol mass spectrometer detection after liquid-liquid extraction. The lower limit of quantification and the higher limit of quantification for DTG are 20 ng/mL and 20.000 ng/mL, respectively.plasma levels will quantified by liquid chromatography coupled with fluorescence detection after liquid-liquid extraction.

Schedule of programmed clinical and laboratory evaluation

	Week					
	-2 Selection	**0 Enrollment**	**4**	**12**	**24**	**48**
Clinical assesment	√	√	√	√	√	√
B/C events	√					
Adherence			√	√	√	√
CD4+ / CD8+	√	√	√	√	√	√
Viral Load (HIV-RNA)	√	√	√	√	√	√
Hematology	√	√	√	√	√	√
Biochemistry	√	√	√	√	√	√
Total, LDL, HDL and Tryglicerids,		√		√	√	√
Plasma Creatinine CPK and Seric Phosfate	√	√	√	√	√	√
Proviral Genotyping (if not previously performed)		√				
Genotipic resistance test and viral tropism		Viral Rebound				
Adverse events			√	√	√	√
PK Studies * (selected patients)	24-hour admisión for pk studies before and 2 weeks after treatment switching					

10 ADVERSE EVENTS

10.1 DEFINITION

Adverse event: (AE) Medical event presented by a patient or clinical research subject administered a pharmaceutical product, and which does not necessarily have a causal relation to the treatment.

Serious adverse event: (SAE) Medical event classified as such and which, regardless of the dose involved:

- causes patient death,
- produces a life-threatening situation for the patient,
- requires or prolongs in hospital admission,
- produces important or persistent incapacitation/handicap, or constitutes a congenital defect or anomaly,
- needs action to prevent any of above situations.
- is considered medically significant

Examples of such events are intensive care in an Emergency Service or in the home in a patient with allergic bronchospasm; blood dyscrasias or seizures not giving rise to hospital admission, or the development of drug dependency or abuse.

Unexpected adverse event: (UAE) AE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

Serious unexpected adverse reaction: (SUSAR) SAE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

10.2 MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until the last study visit or to 28 days after the last dose of IMP in case of early withdrawal while patient is receiving IMP. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to the Sponsor (see contact details at the end of the paragraph) within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate

method, using the SAE Report Form (attachment N, can be found in the Investigator's File), or approved equivalent form.

10.3 DOCUMENTATION RELATED TO AE AND SAE

Each AE and SAE to take place during the study should be documented in the medical records of the patient in accordance with standard clinical practice of the researcher, and in the CRF. For each SAE, an independent set of SAE form will be used independently. Only if there are multiple SAE at the time of the initial report and these are temporary and / or clinically interrelated can be registered on the same set of SAE form.

The researcher should try to make a diagnosis of the event based on the signs, symptoms and / or other clinical information. An AE diagnosis has to be recorded per line or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialed and dated by the investigator.

SAE pages found in the investigator's file shall be completed as precisely as possible, printed and shall be signed by the investigator before being sent to the sponsor. It is very important that the initial page SAE researcher provide its opinion in regard to the relationship of the event to the study drug.

10.4 EVALUATION OF ADVERSE EVENTS

A qualified Investigator will evaluate all AEs as to:

10.4.1 Seriousness

A SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.

- An elective treatment of a pre-existing condition unrelated to the studied indication.

- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

10.4.2 Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

Intensity will be assessed by the investigator using the following terms according to the Division of AIDS table for grading the severity of adult and pediatric adverse events (Attachment O):

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life threatening
- Grade 5 = Death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.4.3 Causality

The causal relation will be established according to the algorithm of the Spanish Pharmacovigilance System, which contemplates the following categories:

Definitive:

- A plausible time sequence exists in relation to administration of the drug or its plasma or tissue concentrations.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.
- The event cannot be explained by the concurrent disease or by other drugs or chemical substances.
- Response to withdrawal must be clinically plausible, i.e., the condition improves on discontinuing administration of the drug.
- A positive response to repeat exposure is observed.

Probable:

- A reasonable time sequence exists in relation to administration of the drug.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.
- The event is unlikely to be explained by the concurrent disease or by other drugs or chemical substances.
- Response to withdrawal is clinically plausible, i.e., the condition improves on discontinuing administration of the drug.
- No repeat exposure is required to complete this definition.

Possible:

- A reasonable time sequence exists in relation to administration of the drug.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.

- The event might be attributable to the clinical condition of the patient or to other concomitantly administered drugs or chemical substances.
- Information concerning drug withdrawal may be unavailable or confusing.

Improbable:

- A clinical event, including anomalous laboratory test findings, with a time relation to administration of the drug which makes a causal association unlikely, and where other drugs, chemical substances or intercurrent disease afford plausible explanations for the observed event.

Unrelated:

- None of the above criteria are met.

10.4.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.4.5 Action Taken

The Investigator will report the action taken with IMP as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of IMP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.4.6 Outcome

SAE will be followed preferably until:

- Resolution of the event;
- Stabilization of the event; or
- Resetting the baseline situation of the event, in case baseline situation is available.

Otherwise, they will continue until:

- The event can be attributed to products other than the study medication or factors unrelated to the study; or
- It is unlikely to obtain further information.

10.5 ABNORMAL LABORATORY VALUES

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Liver Chemistry Stopping and Follow up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of IP and the follow-up period. IP will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin; bilirubin fractionation required)
    - NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria;

- ALT ≥8xULN;

- ALT ≥3xULN (if baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;

• ALT ≥3x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;

• ALT ≥5xULN and 2 weeks (with bilirubin 2 weeks; Subjects who develop ALT ≥5xULN should be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When liver chemistry stopping criterion is met, do the following:

- **Immediately discontinue DTG and withdraw the subject from the study. Subjects should not restart DTG due to the risk of a recurrent reaction.**

- Report the event to the study Sponsor within 24 hours of learning its occurrence (see
- [See Section10.7 Expedited Reporting of Adverse Events).
- Complete the liver event CRF and SAE CRF, where applicable, (see Section 10.7.3 Reporting by Sponsor to ViiV Healthcare).
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed;
- Perform liver event follow up assessments (described below), and monitor the
- subject until liver chemistries resolve, stabilize, or return to baseline values as
- described below;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for
- repeat liver chemistries, liver event follow up assessments (see below), and close monitoring;
- A specialist or hepatology consultation is recommended;
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline
- phosphatase, bilirubin) resolve, stabilize or return to within baseline values;

Consider the following additional tests to further evaluate the liver event:

1. Viral hepatitis serology including:
   - Hepatitis A IgM antibody;
   - HBsAg and Hepatitis B Core Antibody (IgM) and DNA;
   - Hepatitis C RNA;
   - Hepatitis E IgM antibody and RNA;
   - Cytomegalovirus IgM antibody and DNA;
   - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing and DNA);

2. Syphilis screening

3. Drugs of abuse screen including alcohol

4. Serum acetaminophen test (APAP adduct test)

5. Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);

6. Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;

7. Obtain complete blood count with differential to assess eosinophilia;
8. Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;

9. Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;

10. Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;

11. Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

10.6 ALLERGIC REACTIONS

Subjects may continue investigational product(s) for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the investigational product(s) should permanently discontinue the investigational product regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

If ABC- containing products will be regularly used as background ART, then subjects should be managed in terms of a clinically suspected ABC hypersensitivity reaction.

10.7 EXPEDITED REPORTING OF ADVERSE EVENTS

10.7.1 Reporting to Regulatory Authorities and the Ethics Committee

The sponsor will inform the Spanish Medicines Agency (Ministry of Health), the competent authorities of the autonomous region and the Ethics Committees implicated in the clinical trial about any important information of security of the IMPs.

The sponsor will inform the Spanish Medicines Agency (Ministry of Health) of any SUSAR which may be related to the study treatment.

The sponsor will inform competent authorities of the implicated autonomous region of any SUSAR which may be related to the study treatment, and that have been happened in patients in its autonomous region.

The sponsor will inform the Ethics Committee of any SUSAR which may be related to the study treatment, and that have been happened in patients included in its sphere of action.

The Sponsor will inform relevant Regulatory Authorities and Ethics Committees;

- Of all relevant information about SUSAR that are fatal or life-threatening as soon as possible and in any case no later than 7 days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days

- Of all other SUSAR as soon as possible, but within a maximum of 15 days of first knowledge by the investigator.

10.7.2 Immediate reporting by Investigator to Sponsor

The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

Contact details for Sponsor

CTU-Clinical Trial Unit
C/ Rosselló, 138, bajos y
C/Mallorca 183.
Tel: 93 227 9877 e-mail:acruceta@clinic.ub.es. FAX 932279877

10.7.3 Reporting by Sponsor to ViiV Healthcare

The Sponsor will supply ViiV Healthcare with a copy of all SAEs which involve exposure to Dolutegracvir within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC) and with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Contact details for ViiV Healthcare:

GSK's Case management Group: Fax +44.20-8754-7822 .

10.7.4 Reporting by Sponsor to Coordinating investigator

The Sponsor will inform the Coordinating investigator of all SAEs within 24 hours in order that the Coordinating investigator can call the scientific committee to assess trial stopping rules.

Contact details for Coordinating investigator

Jose M. Miro Meda (PI), MD, PhD, Consultant, Infectious Diseases Service, Hospital Clínic/IDIBAPS, University of Barcelona, Barcelona, Spain

Villarroel, 170, 08036 Barcelona, Tel. 93 227 5430, Fax: 93 227 9877 E-mail: jmmiro@ub.edu

11 STATISTICS

Statistical Analysis Plan (JO)

The number of cases to perform the DDI studies range between 5 and 10. For the efficacy and safety study, since this is an exploratory single-arm clinical trial there is no formal power calculation. although 20 patients will be included in the study

To assess the effects of DTG on the pharmacokinetics of immunosuppressant drugs (Cyclosporine A, Tacrolimus, Syrolimus and Mycophenolic acid), the 90% CI for the geometric mean of the test (after drug administration with DTG)/reference (before drug administration with DTG) ratio for the parameters Cmax, Cmin, Tmax and AUC were computed using two one-sided t tests.

The changes are expressed as mean (standard deviation) or median [interquartile range] according to normal and non normal distributions. To assess intragroup changes, we were used repeated measures t-test or Wilkoxon signed rank test, as appropriated.

To assess the efficacy and safety of dolutegravir-based antiretroviral treatment, a descriptive analysis will be performed, showing the the proportion of patients with plasma VL<50 copies at 24 and 48 weeks, the median (IQR) CD4 T cell counts at the same time points and the proportion of patients who needed to stop dolutegravir due to WHO grade III or IV adverse events.

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Researchers and institutions will allow the monitoring, and audits by the Health Authorities or the Sponsor giving direct access to data and original source documents.

Access to personal patient information will be restricted to the Study physician / staff. To allow monitoritings, audits and inspections, access to data to Health Authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee and personnel authorized by the Sponsor, is guaranteed while maintaining the confidentiality thereof according to current legislation.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 STUDY MONITORING

In accordance with applicable regulations and Good Clinical Practice (GCP), the monitor will visit or contact the center on a regular basis. The duration, nature and frequency of visits / contacts depend on the monitoring plan.

During these contacts, the monitor shall:

- monitor and evaluate the progress of the study;
- examining the data collected;
- carry out a verification of the source documents;
- identify any problems and find solutions;

The goal of the monitoring activity is to verify that:

- the rights and welfare of subjects are respected;
- survey data are accurate, complete and verifiable with the help of original documents;
- the study is performed according to the protocol and any amendment adopted, GCPs and regulations.

The investigator must agree to:

- grant to monitor direct access to all relevant documentation;
- devote part of his/her time and staff time to the monitor in order to discuss the results of the monitoring, as well as any other possible aspect.

The monitor should also contact the center before starting the study with the aim to discuss with staff the Protocol and procedures for data collection.

13.2 AUDITS AND INSPECTIONS

Sponsor can carry out an audit of quality control at its sole discretion. In this case, the investigator should agree to grant the auditor direct access to all relevant documentation and devote part of his/her time and staff time to the auditor in order to discuss the results of the monitoring, as well as any other possible aspect.

Moreover, regulatory authorities may also inspect the study. In this case, the investigator should agree to give the inspector direct access to all relevant documentation and devote part of his/her time and staff time to the inspector in order to discuss the results of the supervision, as well as any other possible aspect.

13.3 CASE REPORT FORM

Data collection will be done through an electronic Medical History with a system of access by username and password. The application has track changes (recording the user that has performed).

Accurate and reliable data collection is ensured by checking and cross checking the Medical History front site records conducted by the study monitor (verification of source documents). The data collected will be added to a computer database which will be reviewed for possible inconsistencies to be resolved by the research team of the study in site.

13.4 ALLOCATION PARTICIPANT IDENTIFICATION CODES

All participants will be assigned with a code that will allow the patient to be identified. The patient code will be assigned correlative at the inclusion of the study (program code centralized, formed by letters and numbers)

14 ETHICS

14.1 GENERAL CONSIDERATIONS

The study will be performed in accordance with the local national laws (Royal Decree 1090/2015), the guidelines of the International Conference on Harmonization (ICH), and the guidelines of the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and amended by subsequent assemblies (last in Fortaleza, Brazil in 2013.

This study will be conducted according to Spanish regulations and the required documentation prior to the start will be:

- Protocol acceptance by the sponsor and the coordinating investigator
- Protocol approval by the Ethics Committee.
- Protocol authorization from the Spanish Drug Agency (Ministry of Health)
- Approval by the Direction of the Institution

All subjects will be guaranteed continued medical and nursing supervision throughout the duration of the study.

This study will conform to the standards of "Good Clinical Practice".

Also, following the “Good participatory practice guidelines” (published by the Joint United Nations Programme on HIV/AIDS (UNAIDS), representatives of the community-based detection centres have participated in the design of the protocol and the Participant Information Sheet, through the Community Advisory Committee (CAC).

14.2 PATIENT INFORMATION SHEET AND INFORMED CONSENT

Informed consent will be obtained before including the patient in the trial. The investigator is to inform the patient of the nature, duration and purpose of the study,

as well as of all the obstacles and inconveniences which – within reason – may be expected from it. Furthermore, the patient is to receive information in writing. The participating patients must be legally competent to give informed consent, with the possibility of taking decisions at his/her own free will. The patient has the right to leave the study at any time.

14.3 PAYMENT TO RESEARCH SUBJECTS

No reimbursement to patients has been planned.

15 DATA HANDLING AND RECORD KEEPING

15.1 DATA HANDLING

The processing of the data to be compiled by the study sponsor during the trial will be subject to current legislation as regards data protection (LOPD, Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal). The patient will be identified in the records by the corresponding code only. The patient is to be guaranteed anonymity, and is to be informed that all communication will take place between him/her and the investigator – not the sponsor of the trial.

Data transmitted to third countries and other countries will in no case contain personal data. In the event that such transfer occurs, it will be for the same purposes of the study described and ensuring confidentiality at least to the level of protection of the law in Spain.

15.2 RECORD KEEPING

CONFIDENTIALITY

Subjects will be codified with a serial numeration. The PI and duly authorized collaborators will compromise to maintain personal data strictly confidential, according to the corresponding National Legislation (Ley de Protección de Datos de Carácter Personal 15/99). The link between the numeric code and real personal data from subjects will be rigorously kept by the PI.

Patient will be informed that their participation in the trial will be treated with the same confidentiality as their clinical documentation, but, if necessary, a member of

the site CREC, an inspector designated by the health authorities, or the clinical trial monitor may have access to those records.

In the case report form, the patient will only be identified by the assigned study code. The name of patients will not appear in any publication or report of the study results.

The participation of the patient in the trial will be noted in their medical records.

The investigator will complete a list which will include the names of the patients participating in the trial, the number of inclusion in the study, and their medical history. Only investigators and the staff responsible for guaranteeing data quality and data analysis will have access to the clinical documentation of the participants.

Duly authorized persons by the sponsor and the health authorities and the Clinical Research Ethics Committee may audit or inspect the trial. Personal information will not be publicly available, in compliance with Organic Act 15/1999, of 13 December, on Personal Data Protection.

Participants may exercise their right to processing, reporting, and transfer of the personal data pursuant to Organic Act 15/1999, of 13 December, on Personal Data Protection. According to the above law, patients can exercise their rights to data access, rectification, opposition, and cancellation, for which they must contact the study doctor.

Only data collected for the study that does not bear any information that could directly identify the patient will be transferred to third parties or other countries. Should this transfer occur, it will be for the same purposes as the study and guarantee confidentiality with at least the level of protection afforded by applicable regulations in Spain.

15.2.1 Investigator file and document retention

The investigator must keep the investigator file with the proper and accurate records to enable the study to be fully documented and data subsequently verified.

The Investigator's study file will contain the protocol and its amendments, CRFs, questionnaires' forms, EC approval and authorization from the health authorities, samples of the patient information sheet and informed consent, staff curriculum, signatures' delegation log and listing of subjects, as well as other appropriate documents and correspondence.

Clinical source documents from subjects (usually predefined by the project to record key efficacy and safety parameters or documents that are not in the clinical record of the hospital) will be filed indicating the number of patient without personal data.

The investigator should retain these documents at least 25 years, according to with Royal Decree 1090/2015, provided that the promoter does not express a greater period.

15.2.2 Source documents and basic data

The information contained in the Medical History will be considered as primary data, except for patient filiation data and lab tests. Patient participation in the study will be collected on medical records, including assigned code number and identification of the different study visits that will take place throughout the study. At the end of the study, a copy of the CRF will be placed on the site.

16 FINANCING AND INSURANCE

16.1 SOURCE OF FINANCING

The study will be funded partially by ViiV Healthcare.

16.2 INSURANCE POLICY

In accordance with Royal Decree 1090/2015, the sponsor has taken out civil liability insurance for this study (see Investigator file)

17 PUBLICATION POLICY

The publication of the trial results shall meet the requirements of Royal Decree 1090/2015 and will follow the consort guidelines.